

## ORIGINAL CONTRIBUTIONS

### Alcohol Intake, Drinking Patterns, and Risk of Prostate Cancer in a Large Prospective Cohort Study

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Alcohol drinking has been extensively studied in relation to prostate cancer, yet findings on the direction of the association are equivocal. Previous studies have not examined drinking patterns. Thus, the authors prospectively evaluated the associations between these factors and risk of incident prostate cancer ( $n = 2,479$ ) in a cohort study of 47,843 US men (1986–1998). The men completed a questionnaire at baseline that included information on consumption of specific types of alcohol and frequency of use. The authors estimated hazard ratios using Cox proportional hazards regression for average alcohol intake and number of days per week on which alcohol was consumed stratified by average weekly intake ( $<105$  g/week vs.  $\geq 105$  g/week). Compared with nondrinking, the hazard ratio for consumption increased slightly from an average of 5.0–14.9 g/day (hazard ratio (HR) = 1.05, 95% confidence interval (CI): 0.94, 1.18) to 30.0–49.9 g/day (HR = 1.13, 95% CI: 0.96, 1.33), but it was not increased at  $\geq 50$  g/day (HR = 1.00, 95% CI: 0.77, 1.31) after adjustment for recent smoking and other factors. Compared with abstainers, risk was greatest among men who consumed an average of  $\geq 105$  g/week but who drank on only 1–2 days per week (HR = 1.64, 95% CI: 1.13, 2.38). These results suggest that moderate or greater alcohol consumption is not a strong contributor to prostate cancer risk, except possibly in men who consume large amounts infrequently.

alcohol drinking; cohort studies; ethanol; prostatic neoplasms; risk

Abbreviations: CI, confidence interval; HR, hazard ratio.

Nearly 60 epidemiologic studies have evaluated the association between alcohol drinking and prostate cancer. Some (1–4) but not all (5–13) case-control studies have observed an increased risk of prostate cancer for greater amounts consumed or longer duration of use. The absolute amount of alcohol consumed is generally not related to prostate cancer incidence or mortality in prospective and record-linkage studies of men not selected for alcoholism (14–25).

However, three prospective studies (26–28) have suggested a direct association. Another suggested an inverse association but was based on very few cases in the highest alcohol category (21).

Because men with liver cirrhosis secondary to excessive alcohol use have lower serum testosterone levels (29), excessive intake might be predicted to be associated with decreased risk of prostate cancer. However, in studies of

alcoholics or heavy drinkers, prostate cancer incidence was not reduced (3, 24, 30) or was increased (31).

Some studies have reported that consumption of specific types of alcoholic beverages—beer (2), wine (22), or liquor (1, 13, 27)—may be associated with a higher risk of prostate cancer, but results are not consistent (32). To our knowledge, no studies have examined whether certain drinking patterns, such as consuming the same total weekly amount of alcohol over a period of one or two days as compared with several days, are differently associated with prostate cancer risk.

Despite the large number of published studies, questions remain about the effects of alcohol use at higher intakes, past use, patterns of use, and type of alcoholic beverage consumed. To address these uncertainties, we prospectively evaluated the association of alcohol intake and alcohol drinking patterns with prostate cancer in a large cohort study.

## MATERIALS AND METHODS

### Study population

Participants were members of the Health Professionals Follow-up Study, an ongoing prospective cohort study of 51,529 men aged 40–75 years at enrollment in 1986. The men completed biennially mailed questionnaires on medical history, diet, and lifestyle factors. Deaths were reported by family members or the postal system or were identified through the National Death Index, which is estimated to have a sensitivity of more than 98 percent (33). The overall follow-up response was 94 percent through 1998. We excluded men who had been diagnosed with cancer (except nonmelanoma skin cancer) before 1986 (4.0 percent) and men who returned an incomplete diet questionnaire in 1986 (3.1 percent); this left 47,843 men. The study was approved by the Human Subjects Committee of the Harvard School of Public Health.

### Ascertainment and classification of prostate cancer cases

For each man who reported a prostate cancer diagnosis on a follow-up questionnaire, we asked for permission to request and review the medical records pertaining to his diagnosis. The response rate for this request was 96 percent. Deaths from prostate cancer were identified as described above for all deaths, and next of kin were asked permission for medical record review. Medical records and pathology reports were obtained for 90 percent of the prostate cancer cases. A study investigator blinded to exposure reviewed the records to confirm the diagnosis. Because the reporting of prostate cancer was found to be accurate, we included in the analysis the remaining 10 percent of cases that were based solely on self-report or a death certificate. We excluded Whitmore-Jewett stage A1 (34) cases, because these cases are susceptible to detection bias due to differential rates of surgery for benign prostatic hyperplasia. From enrollment in 1986 through January 31, 1998, 2,479 cases of incident non-stage-A1 prostate cancer were confirmed in 533,047 person-years of follow-up. Of these cases, 608 were advanced (stage C or D) or fatal.

### Assessment of alcohol intake

The semiquantitative food frequency questionnaire that participants completed at baseline consisted of questions on the frequency of consumption of listed portion sizes of 131 food items over the past year, including beer, red wine, white wine, and liquor. This method of assessing alcohol use has been shown to be valid ( $r = 0.8$  in comparison with 2 weeks of diet records; predicts a 0.3-mg/dl increase in serum high density lipoprotein concentration per gram of alcohol intake ( $r = 0.35$ )) and reproducible ( $r = 0.92$  for food frequency questionnaires completed 1 year apart) in this cohort (35). We multiplied servings of specified portions of each type of alcoholic beverage by grams of ethanol per serving (beer = 12.8 g, red and white wine = 11.0 g, and liquor = 14.0 g) and summed the data for the different types of alcohol to obtain total alcohol intake in grams per day.

Participants were also asked about the number of days of the week on which they usually consumed alcohol and whether they had changed their level of alcohol intake in the past 10 years. Former drinkers were defined as men who did not currently drink alcohol but who reported that they had decreased their alcohol intake in the past 10 years. We obtained updated information on alcohol intake from the food frequency questionnaires administered 4 and 8 years after baseline. In 1988, we asked participants about the number of drinks they had consumed per week at ages 18–22 years.

### Statistical analysis

We directly computed age-standardized mean values and proportions for demographic and other factors by category of average daily alcohol intake. We calculated Mantel-Haenszel summary rate ratios and 95 percent confidence intervals for the categories of 0.1–4.9, 5.0–14.9, 15–29.9, 30–49.9, and  $\geq 50$  g/day relative to nondrinking (never drinkers plus former drinkers). Using Cox proportional hazards regression, we estimated multivariable hazard ratios, adjusting for risk factors previously identified in this cohort: body mass index (weight (kg)/height (m)<sup>2</sup>—ordinal) at age 21 years; height (inches—ordinal); cumulative cigarette smoking in the past decade (pack-years—indicator variables for 0, 0.1–5, 5.1–10, 10.1–20, and  $\geq 20.1$  pack-years); family history of prostate cancer; major ancestry (Scandinavian, Southern European, other White, other race); diabetes mellitus; vasectomy; vigorous physical activity (metabolic equivalent-hours/week—ordinal); total energy intake (kcal/day—ordinal); intakes of tomato sauce, red meat, and fish (servings/day—ordinal); energy-adjusted intakes of calcium (mg/day—ordinal), fructose (g/day—ordinal), and  $\alpha$ -linolenic acid (g/day—ordinal); and high intake ( $\geq 15$  mg/day) of vitamin E (mostly supplement users). Ordinal variables had five levels, except fish, which had four levels. None of these variables was a strong confounder. To account for any lack of proportionality in the hazards across follow-up, we fitted separate baseline hazards for groups defined by age and calendar period.

We used baseline alcohol intake in the main analysis, and in alternative analyses we used simple updating (i.e., a time-

varying covariate) or cumulative average updating (i.e., mean of the reported intakes for all preceding food frequency questionnaires (36)) of alcohol intake. To test for trend, we entered into the model a single ordinal variable, which we evaluated by the Wald test. To limit the likelihood that men without a diagnosis of prostate cancer had an occult prostate tumor during follow-up, in an alternative analysis we included person-time at risk only for noncases who had had a prostate-specific antigen test by 1998.

We evaluated whether prostate cancer risk was associated with drinking patterns by combining reported quantity consumed, using one term for lower intake (<105 g/week, or on average <15 g/day) and a second term for higher intake ( $\geq 105$  g/week), with number of days per week on which alcohol was consumed. We examined whether prostate cancer risk differed by type of alcoholic beverage consumed by simultaneously entering into the model terms for wine, beer, or liquor. Beginning follow-up in 1988, we evaluated the weekly number of alcoholic drinks consumed at ages 18–22 years with and without adjusting for current alcohol intake.

We created stratified models to assess whether the association between alcohol intake (g/day) and prostate cancer varied by: susceptible subgroup—age at diagnosis ( $\leq 60$  years vs.  $> 60$  years) and family history of prostate cancer; a metabolic pathway inhibited by alcohol—folic acid (<400  $\mu\text{g/day}$  vs.  $\geq 400$   $\mu\text{g/day}$ ); sources of pro-oxidants—cigarette smoking in the past 10 years and diabetes mellitus; and sources of antioxidants—intakes of vitamin E (<15 mg/day vs.  $\geq 15$  mg/day) and tomato sauce ( $\leq 0.14$  servings/day vs.  $> 0.14$  servings/day). To test for multiplicative interaction, we entered main-effect terms along with a cross-product term for alcohol and each factor, the coefficient for which was evaluated by Wald test. Analyses were performed using SAS, release 6.12 (SAS Institute, Inc., Cary, North Carolina).

## RESULTS

### Selected characteristics by alcohol intake

In 1986, 76.4 percent of the men reported drinking alcohol; 2.9 percent consumed  $\geq 50$  g/day. Men who consumed greater amounts of alcohol were more likely to have smoked in the past decade and to have had a vasectomy, and they consumed more red meat, but they had lower intakes of calcium, fructose, and lycopene (table 1).

### Associations using baseline alcohol intake

In comparison with nondrinkers (never drinkers plus former drinkers), risk of prostate cancer increased slightly in the age-adjusted and multivariable models through 30–49.9 g/day, though risk was not elevated among men who consumed  $\geq 50$  g/day (table 2). The pattern was similar after excluding nondrinkers and using as the reference group those who consumed an average of 0.1–4.9 g/day (table 2). When former drinkers were excluded from the reference group, the association for alcohol intake was comparable to that in the main analysis (for 30–49.9 g/day, hazard ratio (HR) = 1.13, 95 percent confidence interval (CI): 0.96, 1.33; for  $\geq 50$  g/day, HR = 0.99, 95 percent CI: 0.75, 1.29). Former

drinkers were not at increased risk of prostate cancer (HR = 1.04, 95 percent CI: 0.88, 1.23). No association between alcohol intake and advanced cancer (table 2), distant metastatic and fatal cancer (table 2), or regionally invasive (stage C2), metastatic (stage D), and fatal cancer (data not shown) was detected when drinkers were compared with nondrinkers or light drinkers. After exclusion of men who had never had a prostate-specific antigen test, the results were compatible with those of the overall analysis (compared with nondrinking, the hazard ratio for 30–49.9 g/day was 1.09 (95 percent CI: 0.93, 1.28)). Risk of prostate cancer did not increase with number of alcoholic drinks consumed per week at ages 18–22 years, even after adjustment for current alcohol intake ( $p$ -trend = 0.83).

### Associations using updated alcohol intake

In contrast to the use of baseline intake, when simple updating was used in the analysis, men who consumed  $\geq 50$  g/day appeared to be at a slightly increased risk of prostate cancer (HR = 1.20, 95 percent CI: 0.97, 1.49) in comparison with nondrinkers ( $p$ -trend = 0.09). Otherwise, the magnitudes of the hazard ratios for the other levels of alcohol intake were similar to those of the baseline analysis. Results using cumulative average updating were similar to those obtained using baseline intake.

### Alcohol drinking patterns and beverage type

Men who drank alcohol on 5–6 days per week had a modestly higher risk of prostate cancer (HR = 1.19, 95 percent CI: 1.04, 1.35) than men who did not drink or who drank on less than 1 day per week (table 3). However, the hazard ratio for men who drank on all 7 days of the week was not elevated (HR = 1.05, 95 percent CI: 0.92, 1.20). These patterns were similar for advanced cases and distant metastatic/fatal cases (table 3). Compared with men who did not drink or who drank on less than 1 day per week, men who consumed lower amounts (<15 g/day on days that they drank) on 5–6 days of the week (<90 g/week) had a suggestive 23 percent higher risk of prostate cancer (figure 1). Men who consumed higher amounts ( $\geq 105$  g/week) on 3–4 or 5–6 days of the week also had a suggestively higher risk of prostate cancer when compared with nondrinkers (figure 1). In both men who consumed <105 g/week and men who consumed  $\geq 105$  g/week, the hazard ratio was attenuated among those who drank on all 7 days of the week. However, men who consumed greater amounts ( $\geq 105$  g/week) on only 1 or 2 days of the week (i.e., who consumed all 105 g over a period of 1 or 2 days) had a higher risk of prostate cancer (HR = 1.64, 95 percent CI: 1.13, 2.38) (figure 1). Note that this group represents 1 percent of the person-time and prostate cancer cases in the cohort.

Risk of prostate cancer was slightly elevated for higher intake of each type of alcohol (table 4). The risk of prostate cancer associated with white wine intake (for 2–5.9 g/day, HR = 1.14, 95 percent CI: 0.98, 1.33) was similar to that associated with total alcohol intake after results were mutually adjusted for red wine, beer, and liquor intake. Red wine

**TABLE 1. Selected characteristics of 47,843 male health professionals in relation to alcohol intake at baseline in 1986, Health Professionals Follow-up Study\***

Characteristic	Alcohol intake (g/day) at baseline					
	0	0.1–4.9	5.0–14.9	15.0–29.9	30.0–49.9	≥50.0
No. of participants	11,306	11,698	13,172	6,018	4,240	1,409
Mean age (years) in 1986	54.8	53.7	54.2	54.1	56.0	55.6
Mean body mass index† at age 21 years	23.1	23.1	23.0	22.9	22.8	22.9
Mean height (inches‡)	70.0	70.0	70.2	70.3	70.3	70.4
Family history of prostate cancer (%)	12.3	11.4	11.8	12.1	11.9	11.5
History of type 2 diabetes mellitus (%)	5.4	3.2	2.2	1.8	2.0	3.2
Vasectomy (%)	18.2	20.0	21.6	24.7	25.2	25.8
Routine PSA§ screening by 1998 (%)	64.0	69.9	70.5	70.9	66.0	62.9
Smoked in the past 10 years (%)	16.1	18.0	21.6	24.5	37.0	40.4
Vigorous physical activity¶ (METs§/week)	10.9	12.6	14.0	14.5	12.3	10.5
Mean intakes						
Energy not from alcohol (kcal/day)	1,923	1,903	1,888	1,938	1,879	1,943
Alcohol (g/day)	0	2.3	9.7	20.1	38.3	71.0
Calcium (mg/day)#	970	925	894	843	781	721
Fructose (g/day)#	54.8	53.5	48.4	44.4	37.6	33.1
Lycopene (μg/day)#	10,203	10,630	10,509	10,607	9,746	9,008
Linoleic acid (g/day)#	11.6	11.5	11.5	11.4	10.6	9.3
α-Linolenic acid (g/day)#	1.12	1.09	1.07	1.06	0.98	0.87
Red meat (servings/week)	6.5	6.3	6.6	7.1	7.8	8.5
Fish (servings/week)	2.1	2.5	2.5	2.6	2.3	2.2
Supplemental vitamin E (IU/day)	84.2	81.1	84.7	89.8	85.6	86.8

\* All data except age were standardized to the age distribution of the study population.

† Weight (kg)/height (m)<sup>2</sup>.

‡ 1 inch = 2.54 cm.

§ PSA, prostate-specific antigen; METs, metabolic equivalents.

¶ Includes running, jogging, racquet sports, swimming, and bicycling.

# Nutrient intakes were adjusted for total energy intake (including energy from alcohol).

intake was not associated with prostate cancer (for 2–5.9 g/day, HR = 0.93, 95 percent CI: 0.77, 1.13).

### Interactions with alcohol intake

The association between alcohol intake and prostate cancer did not vary by age at diagnosis or by intake of folic acid, vitamin E, or tomato sauce. However, the association of alcohol with advanced and metastatic/fatal disease was stronger in men who were younger (<60 years old) at diagnosis (*p*-interaction values were 0.03 and 0.07, respectively) and in men who had a higher intake (>0.14 servings/day) of tomato sauce (*p*-interaction values were 0.02 and 0.07, respectively). Risk of prostate cancer associated with alcohol consumption was greater among men with type 2 diabetes mellitus (*p*-interaction = 0.08). Among men with diabetes (175 prostate cancer cases), in comparison with nondrinkers, the hazard ratios were 1.09 for 0.1–4.9 g/day, 1.27 for 5.0–14.9 g/day, 1.92 for 15.0–29.9 g/day, 1.37 for 30–49.9 g/day, and 2.48 for ≥50 g/day (*p*-trend = 0.05). For men without diabetes, the association was similar to the overall associa-

tion. A positive relation between alcohol and prostate cancer was evident primarily for men without a family history (*p*-interaction = 0.13). A suggestion of an increased risk of prostate cancer and metastatic/fatal disease with higher alcohol consumption was observed for men who had not smoked in the past decade (*p*-interaction values were 0.14 and 0.03, respectively).

### DISCUSSION

In this large, prospective study, we observed a small and statistically nonsignificant overall increase in risk of prostate cancer with increasing amount and frequency of alcohol intake. However, men who drank alcohol at the highest level (≥50 g/day), men who drank at the highest frequency (7 days/week), and men who were former drinkers were not at increased risk. The 1.64-times higher risk of prostate cancer among men who consumed greater amounts (≥105 g/week) over a period of only 1 or 2 days per week requires further assessment. The association of alcohol intake with prostate cancer was stronger among men with type 2 diabetes

**TABLE 2. Hazard ratios for prostate cancer in relation to average daily alcohol intake at baseline among 47,843 men, Health Professionals Follow-up Study, 1986–1998**

Alcohol intake (g/day)	No. of cases	No. of person-years	Age-adjusted RR*	95% CI*	Multivariate† HR*	95% CI	Multivariate‡ HR	95% CI
<b>All cases</b>								
0	576	126,370	1.00§		1.00§			
0.1–4.9	537	131,714	0.97	0.86, 1.09	0.99	0.87, 1.11	1.00§	
5.0–14.9	694	146,779	1.08	0.97, 1.21	1.05	0.94, 1.18	1.07	0.95, 1.20
15.0–29.9	336	66,794	1.18	1.03, 1.35	1.13	0.98, 1.31	1.14	0.99, 1.31
30.0–49.9	266	45,895	1.17	1.01, 1.36	1.13	0.96, 1.33	1.13	0.96, 1.33
≥50.0	70	15,495	0.95	0.74, 1.22	1.00	0.77, 1.31	0.99	0.75, 1.29
<i>p</i> -trend			0.08		0.20		0.52	
<b>Advanced cases¶</b>								
0	154	128,111	1.00§		1.00§			
0.1–4.9	118	133,330	0.80	0.63, 1.02	0.85	0.67, 1.09	1.00§	
5.0–14.9	175	148,814	1.01	0.82, 1.26	1.02	0.81, 1.28	1.22	0.96, 1.55
15.0–29.9	80	67,766	1.03	0.79, 1.35	1.04	0.78, 1.38	1.24	0.92, 1.67
30.0–49.9	81	62,452	1.01	0.77, 1.31	0.99	0.73, 1.33	1.17	0.85, 1.61
≥50.0								
<i>p</i> -trend			0.41		0.70		0.51	
<b>Distant metastatic or fatal cases¶</b>								
0	67	128,560	1.00§		1.00§			
0.1–4.9	47	133,644	0.74	0.51, 1.08	0.83	0.57, 1.21	1.00§	
5.0–14.9	79	149,279	1.06	0.77, 1.47	1.09	0.78, 1.57	1.32	0.91, 1.92
15.0–29.9	27	68,036	0.81	0.52, 1.27	0.85	0.53, 1.35	1.01	0.62, 1.63
30.0–49.9	38	62,658	1.08	0.73, 1.61	1.09	0.69, 1.71	1.35	0.83, 2.21
≥50.0								
<i>p</i> -trend			0.44		0.62		0.46	

\* RR, relative risk; CI, confidence interval; HR, hazard ratio.

† Hazard ratio was adjusted for current age, body mass index at age 21 years, height, pack-years of smoking in the previous decade, family history of prostate cancer, major ancestry, diabetes, vasectomy, vigorous physical activity, and intakes of total energy, calcium, fructose, tomato sauce, red meat, fish, vitamin E (>15 mg/day), and  $\alpha$ -linolenic acid.

‡ Model included current drinkers only; light drinkers (0.1–4.9 g/day) were used as the reference category. Hazard ratios were adjusted for all covariates controlled for in the above model.

§ Referent.

¶ The top two categories were combined because of small numbers of cases.

mellitus. A slightly increased risk of prostate cancer was noted for increasing amounts of each type of alcoholic beverage consumed, except for red wine intake, for which there was no association.

Our results are compatible with those of two prospective studies (26, 27). In a study of Iowa men (101 cases), the relative risks for 22–92 g/week and ≥92 g/week were 2.1 and 1.5, respectively (26). In a subset of the Harvard Alumni Health Study (366 cases), the relative risks for 1–<3 drinks/day (~13–<39 g/day) and ≥3 drinks/day were 1.85 and 1.33, respectively (27). The magnitude of association was lower in our study than in these two studies. A similar risk pattern emerged in the three studies: Risk in the top category was lower than risk in the next-to-highest category. However, the lower cutpoints for the top category were very different in

the three studies (13.1 g/day (26), ~39 g/day (27), and 50 g/day in this study). In contrast, in 10 distinct prospective or record-linkage studies (16–20, 22–25, 37), investigators did not observe associations between total alcohol intake and prostate cancer. Alcohol use in young adulthood was not associated with prostate cancer in our study or elsewhere (27, 38).

Our results are also consistent with those of two meta-analyses (39, 40). Dennis (39) obtained relative risks of 1.15 (95 percent CI: 1.00, 1.32) and 1.21 (95 percent CI: 1.05, 1.39) for consumption of three and four drinks per day, respectively. The relative risks were 1.04 and 1.06 (not statistically significant) for three eligible prospective studies. Bagnardi et al. (40) reported relative risks of 1.09 (95 percent CI: 1.02, 1.17) and 1.19 (95 percent CI: 1.03,

**TABLE 3. Hazard ratios for prostate cancer in relation to average weekly drinking frequency at baseline among 47,843 men, Health Professionals Follow-up Study, 1986–1998**

Drinking frequency (days/week)	No. of cases	No. of person-years	Age-adjusted RR*	95% CI*	Multivariate† HR*	95% CI
<b>All cases</b>						
0	785	183,093	1.00§		1.00§	
1–2	608	142,289	1.07	0.96, 1.19	1.05	0.94, 1.16
3–4	335	76,112	1.10	0.96, 1.25	1.05	0.92, 1.20
5–6	358	65,395	1.25	1.11, 1.42	1.19	1.04, 1.35
7	393	66,158	1.10	0.97, 1.24	1.05	0.92, 1.20
<i>p</i> -trend			0.008		0.10	
<b>Advanced cases</b>						
0	205	185,423	1.00§		1.00§	
1–2	136	144,197	0.91	0.73, 1.13	0.91	0.73, 1.14
3–4	88	77,016	1.10	0.85, 1.41	1.11	0.86, 1.44
5–6	92	66,384	1.22	0.96, 1.56	1.16	0.90, 1.51
7	87	67,453	0.94	0.73, 1.21	0.84	0.64, 1.11
<i>p</i> -trend			0.51		0.90	
<b>Distant metastatic or fatal cases</b>						
0	92	185,977	1.00§		1.00§	
1–2	52	144,578	0.79	0.56, 1.11	0.83	0.59, 1.18
3–4	35	77,261	0.99	0.67, 1.47	1.00	0.67, 1.51
5–6	41	66,648	1.22	0.85, 1.17	1.18	0.80, 1.75
7	38	67,712	0.89	0.61, 1.29	0.76	0.51, 1.14
<i>p</i> -trend			0.73		0.67	

\* RR, relative risk; CI, confidence interval; HR, hazard ratio.

† Hazard ratio was adjusted for current age, body mass index at age 21 years, height, pack-years of smoking in the previous decade, family history of prostate cancer, major ancestry, diabetes, vasectomy, vigorous physical activity, and intakes of total energy, calcium, fructose, tomato sauce, red meat, fish, vitamin E (>15 mg/day), and  $\alpha$ -linolenic acid.

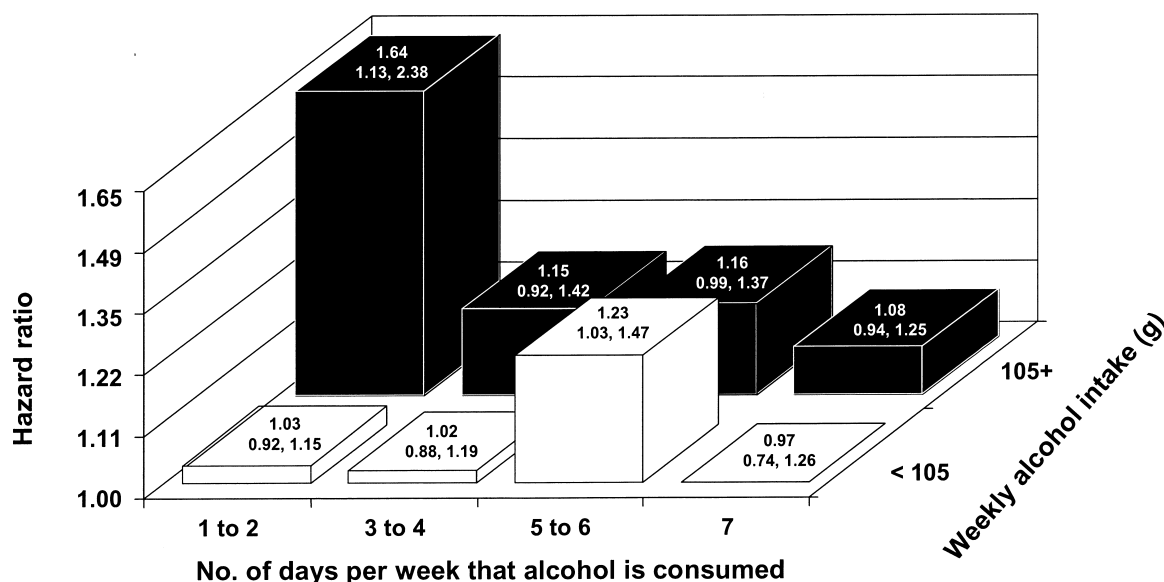
§ Referent.

1.37) for 50 g/day (~3–4 drinks daily) and 100 g/day (~6–8.5 drinks daily), respectively. Because of the timing of publication, the meta-analyses did not include two of the prospective studies that had positive findings (26, 27).

Ethanol may be predicted to have both adverse and beneficial effects on prostate carcinogenesis. The major metabolic pathway for ethanol is conversion to acetaldehyde by alcohol dehydrogenase, followed by conversion of acetaldehyde to acetate by acetaldehyde dehydrogenase (41). However, with high intake, other metabolic pathways may play a more prominent role. Superoxide and hydroxyethyl radicals are generated from the metabolism of acetaldehyde by xanthine oxidase in the liver (42) and possibly also in the prostate (43). Alcoholics have greater oxidative stress as measured by levels of hydroxyethyl and malondialdehyde protein adducts in circulation (44). In animal models, chronic ethanol intake results in higher lipid peroxidation in the prostate (45). Acetaldehyde inhibits enzymes in the DNA methylation pathway (46, 47). Superoxide generated in the

metabolism of acetaldehyde increases folate catabolism, which may explain folate deficiency in alcoholics (42). The greater production of reactive oxygen species and reduced availability of methyl groups for promoter methylation may together contribute to a higher risk of prostate cancer among chronic drinkers or binge drinkers. Although it is plausible, we did not observe effect modification by folic acid intake. Other possible adverse effects of alcohol that might influence prostate cancer risk include enhancement of the solubility and absorption of mutagens and inhibition of cytochrome P-450 detoxification enzymes (48).

Alcohol intake alters sex hormone levels into profiles that would be predicted to decrease risk of prostate cancer. Experimentally, repeated high-dose ethanol intake in nonalcoholic men suppresses testicular production and increases clearance of testosterone (49–51), though these effects are transient (51). With sustained alcohol abuse, testicular atrophy may lead to lower concentrations of circulating testosterone (29). Alcohol also increases circulating estrogen



**FIGURE 1.** Hazard ratios and 95% confidence intervals for prostate cancer in relation to number of days per week on which alcohol was consumed, by weekly alcohol intake at baseline, Health Professionals Follow-up Study ( $n = 47,843$ ), 1986–1998. The reference category was nondrinkers.

levels, possibly through enhanced aromatization of androgens to estrogens in the liver (52). Circulating levels of sex hormone-binding globulin, which is the major carrier of testosterone and estradiol in circulation, are also higher among alcoholics (53). In rodent models, chronic high-dose ethanol ingestion results in reduced prostate weight and atrophy of the prostate epithelium (54), which again would be expected to reduce risk of prostate cancer. Excessive alcohol use (55) and possibly moderate intake (56) may also be associated with lower circulating levels of insulin-like growth factor 1, a purported prostate cancer risk factor (57). If it is causal, the slight positive association between moderate-to-high consumption of alcoholic beverages and prostate cancer observed in our study may reflect a small outweighing of detrimental effects relative to beneficial effects of ethanol on the prostate. At higher levels of alcohol intake, where risk of prostate cancer was not increased, the damage due to reactive oxygen species generated in the metabolism of ethanol may be balanced against the reduced promotional activity of suppressed androgens. However, studies of alcoholics or heavy drinkers have not provided support for an inverse association (3, 24, 30, 31).

The increased oxidative stress hypothesis implies that alcohol would act early in the prostate carcinogenesis pathway, and thus alcohol would affect the overall incidence of prostate cancer. The hormone hypothesis implies that alcohol would reduce hormonal promotion of the growth of prostate tumors. Compatible with these hypotheses, in our study we observed a higher risk of prostate cancer associated with alcohol drinking, and risk was not greater for advanced

disease. In our previous studies of prostate cancer in this cohort, risk factors that would be expected to promote the growth of already-initiated prostate tumors, such as fat and red meat intake (58), were more strongly associated with advanced disease. Alternatively, factors that would be expected to influence oxidative burden, like intake of tomato sauce (which contains lycopene), appear to be associated across the spectrum of severity of this disease (59). In Iowa men, a positive association was observed for alcohol intake and local and regional/distant disease (26). In the Netherlands Cohort Study, risk was increased for both local and advanced tumors for specific types of alcohol; however, none of the associations were significantly linearly increasing (22).

We observed that risk of prostate cancer increased with increasing number of days on which alcohol was consumed. However, men who drank alcohol on all days of the week (their mean daily intake was 36.9 g) were not at increased risk. Whether men who drank daily did not have an increased risk because they have sustained depression of testosterone relative to estrogen needs further evaluation. Interestingly, men with a drinking pattern reflecting infrequent intake of a high amount of alcohol had 1.64 times the risk of nondrinkers. These men routinely consumed at least 105 g of alcohol on 1 or 2 days of the week. Their pattern of consumption may result in different metabolic pathways' being activated or deactivated or different hormonal profiles (transient vs. sustained) in comparison with men who had a drinking pattern reflecting frequent intake of small amounts. Again, however, we cannot preclude that this was a chance

**TABLE 4. Hazard ratios for prostate cancer in relation to average daily intakes of wine, beer, and liquor at baseline among 47,843 men, Health Professionals Follow-up Study, 1986–1998**

Alcoholic beverage intake (g/day)	No. of cases	No. of person-years	Multivariate* HR†	95% CI‡
Nondrinkers	576	126,370	1.00‡	
Wine				
0.1–0.9	310	64,301	1.08	0.95, 1.23
1.0–1.9	403	94,819	1.00	0.88, 1.13
2.0–5.9	489	83,858	1.10	0.96, 1.25
≥6.0	346	75,090	1.16	0.93, 1.21
<i>p</i> -trend			0.29	
Beer				
0.1–0.9	458	94,966	1.03	0.92, 1.16
1.0–1.9	251	60,994	1.00	0.86, 1.15
2.0–5.9	327	74,716	1.07	0.94, 1.22
≥6.0	265	65,284	1.13	0.98, 1.31
<i>p</i> -trend			0.05	
Liquor				
0.1–1.9	331	84,759	1.01	0.88, 1.15
2.0–5.9	182	46,040	0.97	0.82, 1.15
5.9–12.0	501	88,402	1.09	0.97, 1.23
≥12.0	393	59,037	1.08	0.95, 1.23
<i>p</i> -trend			0.21	

\* Hazard ratios were adjusted for current age, body mass index at age 21 years, height, pack-years of smoking in the previous decade, family history of prostate cancer, major ancestry, diabetes, vasectomy, vigorous physical activity, and intakes of total energy, calcium, fructose, tomato sauce, red meat, fish, vitamin E (>15 mg/day), and  $\alpha$ -linolenic acid. Individuals were entered into the analysis for each type of alcoholic beverage that they consumed. Indicator variables for each type of alcoholic beverage were simultaneously entered into the model.

† HR, hazard ratio; CI, confidence interval.

‡ Referent.

observation due to a small sample size in that subgroup (30 cases in 5,343 person-years).

We did not observe notable differences in risk of prostate cancer by type of alcoholic beverage consumed, with the exception of red wine, for which there was no association. Findings have not been consistent among studies examining different types of alcoholic beverages (1, 2, 13, 22, 27).

Risk of advanced prostate cancer associated with alcohol intake was greater among men who were younger at diagnosis, though age did not modify the association for prostate cancer. If alcohol acts early in prostate carcinogenesis, an association with advanced disease might be more observable in younger men because of a shorter span between the initiation of the tumor and progression. Although we had hypothesized that risk of prostate cancer associated with alcohol intake would be greater among men with a higher oxidative burden, there was no difference in this association by level of

intake of vitamin E or tomato sauce. Furthermore, risk of more advanced disease with alcohol intake was greater for those who had not smoked in the past 10 years or who had a higher intake of tomato sauce. It is possible that the findings for more advanced disease are false-positive, given that these analyses contained fewer cases.

The positive association of alcohol intake with prostate cancer appeared to be greater among men with type 2 diabetes mellitus. Men with diabetes exhibit greater oxidative damage (60, 61), which may be worsened by chronic alcohol use (62). In addition, in diabetic rats with low insulin and high glucose levels, liver aldehyde levels are increased and aldehyde dehydrogenase activity is reduced (63). If this is also true in humans with type 2 diabetes, the accumulation of aldehydes such as acetaldehyde may overwhelm primary metabolic enzymes that detoxify aldehydes. Secondary metabolic pathways, such as the xanthine oxidase pathway (42, 43), may be important contributors to a greater abundance of reactive species among persons with diabetes, thus possibly enhancing their prostate cancer risk.

We included in the analysis 3.5 times more cases than the next-largest study on this topic. We adjusted for suspected risk factors for prostate cancer, including cigarette smoking (a risk factor for fatal disease), a strong correlate of alcohol use. Although we cannot rule out confounding by unknown factors that differ between nondrinkers and drinkers, after exclusion of the nondrinkers the results were compatible with the overall findings. We administered a food frequency questionnaire for which alcohol assessment was valid and reliable (35). Because alcohol intake was assessed years prior to diagnosis, it is unlikely that the extent of error in the reporting of alcohol differed by disease status. To account for changing levels of alcohol intake over time and to increase accuracy for long-term intake, in a subanalysis we used simple and cumulative average updating of alcohol intake from three food frequency questionnaires with data collected 4 years apart. The increased risk among men consuming ≥50 g/day observed when simple updating was used but not when baseline or cumulative average updating was used might indicate that very recent high alcohol intake is important. However, this approach may be more prone to bias due to preclinical disease. It is unlikely that there was bias due to health-conscious men's being those who both moderately drink alcohol and undergo prostate-specific antigen screening, because a high percentage of men had already been screened, and results were unchanged in a subanalysis that included only those men who had had a prostate-specific antigen test.

Overall, alcohol does not appear to be a strong contributor to prostate cancer risk, except possibly in men who consume large amounts infrequently and in men with type 2 diabetes mellitus. Additional study is needed for these groups.

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